QUANTIFYING THE INDIRECT EFFECTS OF *HAEMOPHILUS INFLUENZAE* TYPE B VACCINATION IN CHILDREN UNDER 5 YEARS-OLD

by

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Abstract

Background

Haemophilus influenzae type b (Hib) is a significant cause of meningitis and pneumonia among children under 5 years. A conjugate vaccine has been available since the mid-1980s, leading to disease reductions well above what would be expected from direct protection of the vaccine alone. This indicates indirect effects provide substantial protection against Hib disease and are a function of population-level vaccine coverage. Indirect effects are rarely investigated because it requires large, cluster randomized trials; instead we used pre-post vaccine introduction studies to model these effects.

Methods

Three methods to perform this analysis were identified in the literature. Wolfson, et al. described a method to compare the observed disease reduction to the reduction expected only from direct effects, resulting in an indirect effect multiplier based on vaccine coverage. Samandari, et al. estimated a multiplier for the number of people effectively protected by vaccination using vaccine coverage and incidence rates before and after vaccination. Lastly, Adegbola, et al. used average ages of Hib infection and vaccination to calculate an alternative estimate of direct protection from vaccination. Eleven studies were used for the Wolfson and Samandari methods and three were used for the Adegbola method.

Results

All three methods suggest a robust indirect effect of Hib vaccine against disease, with > 90% disease reduction predicted at only 70% coverage. Indirect effects were most influential at vaccine coverages below 40%, as vaccinating one child protected anywhere

from two to six others. Direct effects dominated at vaccine coverages above 60%. Validating these results against an infectious disease theoretical framework and a study that empirically examined indirect effects on an individual level confirmed the accuracy of our results.

Conclusion

Predicted protection varied between the methods, but all demonstrated the importance of indirect effects at low vaccine coverage. These results can be used to better estimate the expected disease reduction prior to beginning a vaccine program and can impact policy decisions regarding vaccination. The models used in this analysis can also be applied to other vaccines, such as pneumococcal conjugate vaccine.

Readers: Dr. David Dowdy and Dr. William Moss

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Introduction

Hib Disease Burden

Haemophilus influenzae type b (Hib) is a bacterium that causes significant morbidity and mortality in children under the age of five years. Responsible for numerous syndromes such as pneumonia, meningitis, and epiglottitis, as well as non-invasive but common diagnoses such as otitis media, Hib was the leading cause of invasive bacterial disease worldwide before the introduction of effective vaccines [1, 2]. Hib is one of the six serotypes of *Haemophilus influenzae* (a-f) but is responsible for about 95% of all invasive disease caused by *Haemophilus influenzae*. It is spread through droplets in the air and colonizes the nasopharynx, where it can be spontaneously cleared, remain without causing symptoms, or invade the bloodstream and cause invasive infection [2].

The burden of disease is almost exclusively in children under five years (U5s), with about two-thirds of it concentrated in children under 18 months and relatively few cases in adults [1]. In the absence of vaccination, the median age of invasive disease is 6-8 months; as with most infectious diseases, median age increases after vaccination programs are established as younger children, who make up the bulk of the cases, are immunized and the disease burden curve shifts [2, 3]. It was estimated that in 1990, Hib caused about 450,000 deaths worldwide in U5s, which declined to about 370,000 in 2000 [4, 5]. This is a small proportion of the approximately 8 million cases of invasive Hib disease in U5s annually and does not accurately reflect the morbidity of Hib-related syndromes such as pneumonia and epiglottis, which have significantly lower mortality rates than meningitis [5]. Although pneumonia is the most common Hib-caused syndrome, meningitis is the most serious syndrome and has the highest case fatality ratio,

up to 20%. While many children live through their encounter with Hib meningitis, not many do so unscathed. Up to 30% of surviving children have various neurological sequelae including seizure disorders and hearing/vision loss, many of which are permanent [2].

Hib Conjugate Vaccine

The introduction of the highly effective Hib conjugate vaccine in the 1980s has led to the virtual disappearance of invasive Hib disease (IHiD) in children U5s from developed nations, though certain disadvantaged populations, such as Native Americans and Australian aboriginals, still have higher rates of disease than the general population due to poverty-associated risk factors [6, 7]. While vaccine uptake in low- and middle-income countries has been slower, almost all countries have now introduced Hib vaccine, with many countries achieving routine immunization of birth cohorts. However, the elevated disease risk among disadvantaged populations also holds in these countries and is exacerbated by reduced vaccination of at-risk populations. This is notable as Hib cases and deaths are concentrated in resource-poor settings, where routine vaccine use was slower to take root, exacerbating pre-existing disparities within and between countries of different economic levels. In 2000, just ten countries, all in Asia or Africa, account for an estimated 61% of childhood Hib deaths [5].

Much of the hesitancy to pursuing routine vaccination in these countries was due to a number of factors, including cost and insufficient disease burden data. Hib is a notoriously difficult organism to culture in the best of lab conditions, so poor lab facilities in many of these countries artificially decreased the measured incidence rate of Hib [2]. Empiric treatment with antibiotics is also common in many of these countries,

and specimens collected after treatment initiation are much less likely to successfully culture Hib. The WHO recommends three doses of Hib vaccine, either with all three doses administered in a primary series or a two dose primary series with a booster dose [1]. Inclusion in the pentavalent vaccine that also includes diphtheria, tetanus, pertussis, and hepatitis b vaccine has helped defray some of the costs of the high number of required doses through reduced cold chain capacity requirements and has also simplified introduction into routine vaccination programs. Additionally, vaccine probe trials, which compared all-cause incidence of meningitis and pneumonia in clusters randomized to Hib vaccine, in Indonesia and the Gambia have demonstrated that Hib is prevalent in these countries and mainly was not lab-confirmed due to difficulty in culturing Hib and widespread empiric antibiotic use [1, 8, 9]. Worldwide Hib deaths have declined by almost 50% in one decade, falling to fewer than 200,000 deaths in the year 2010 [4]. This is most likely due to increasing quality of health systems and wider vaccine use in high-burden settings.

The Hib vaccine provides almost complete protection against invasive Hib disease, with direct efficacy estimates ranging from 95-100% [2]. Additionally, the vaccine has been shown to provide excellent indirect protection in addition to direct protection, leading to the elimination of Hib-associated disease much faster than other childhood vaccine-preventable diseases [10, 11]. Vaccination programs rely on indirect protection to establish herd immunity, or the protection of unvaccinated people due to high vaccine coverage in the population as a whole [12]. These indirect effects start to build as vaccine coverage increases and are most pronounced at medium coverage levels; at low coverage, there are not enough vaccinated children to reduce transmission, and at

very high coverage, almost all children are being protected directly by vaccination. Some pathogens, such as measles, require 95% vaccine coverage to achieve disease elimination, but strong indirect effects leading to herd immunity have been seen even at Hib vaccine coverage levels as low as 40-50% [10, 13-17]. Herd protection is clearly an important factor in understanding the full benefit of a routine immunization programs and eliminating Hib disease, but few attempts have been made to quantify the indirect effects of Hib vaccine.

Indirect Effects

Indirect effects can only be quantified in a few study designs. Rather, they are assumed to be notable post hoc when observed disease reduction is greater than what would be expected from direct effects alone at that vaccine coverage level. Hib vaccine reduces the risk of nasopharyngeal colonization as well as the risk of disease. In addition to standard herd immunity effects, the reduction of nasopharyngeal colonization in vaccinated individuals may further protect unvaccinated individuals from transmission and colonization, leading to less disease and explaining the strong indirect effects seen with Hib vaccine [18-20]. While some research has focused on understanding the biological mechanism of indirect protection, there is a dearth of information about the exact size of indirect effects and how they affect population level disease dynamics. Within this limited body of literature, little work has been done to understand how indirect effects can fluctuate as vaccine coverage changes, though this research is becoming more widespread [16, 21].

Much of the reticence to empirically investigate indirect effects can be attributed to the need for large, complicated study designs, namely cluster randomized trials. These

studies randomize groups of people to the Hib vaccine or placebo arm and can compare the rates of disease in the unvaccinated people on the vaccine arm to the rates in unvaccinated people in the placebo arm to arrive at an understanding of the level of indirect protection provided by the vaccine. Because the unit of analysis in these trials is the cluster and not the individual, they require a sample size inflation that can vastly increase the already sizeable cost of a clinical trial [22, 23]. Newer study designs, such as stepped wedge trials, have been developed to examine indirect effects of vaccination as in The Gambia with hepatitis B vaccine [24]. However these trials require substantially more time to fully roll out when compared to a typical parallel design, again increasing the cost of a clinical trial.

Ideally, it would be desirable to have empirical evidence of the level of indirect protection from Hib vaccine against IHiD to inform vaccine rollout policies, especially in resource-poor settings. Factoring in the indirect protection provided by a vaccine could help administrators estimate the true level of vaccine coverage necessary to reduce disease by a certain amount. An indirect effect multiplier could be included in the vaccine effective coverage formula (vaccine efficacy * vaccine coverage) to predict the disease reduction due to direct and indirect effects of the vaccine in a population with certain vaccine coverage levels. A multiplier of one would indicate that disease reduction was completely due to direct effects of the vaccine, whereas anything larger would suggest the involvement of indirect effects in protection against IHiD. This could make vaccine programs more cost-effective and also inform when supplemental vaccination campaigns might be necessary in a given setting, making distribution of costlier vaccines more efficient. WHO universally recommends Hib vaccine worldwide, and all but two

countries have achieved uptake, but the ideal target vaccine coverage levels remain uncertain [1].

Due to the lack of funding for and interest in quantifying indirect effects within a large trial, we chose to use observational studies already available in the literature to understand the varying levels of herd protection based on total U5 vaccine coverage. Using available studies can provide an answer in settings where it is infeasible to conduct a cluster randomized trial or stepped wedge trial while still allowing for the calculation of indirect effects using real-world data. These estimates are also necessary for etiological modeling work that incorporates vaccine effective coverage, which usually only estimate direct protection. Previously, the only studies that have specifically examined herd protection as a function of Hib vaccine coverage used primary data; the use of secondary data to evaluate Hib indirect effects as a function of coverage has not formally been attempted.

Methods

Literature Search

The studies used for this analysis were vaccine impact studies included in the literature review for Hib Global Burden of Disease (GBD) estimates currently being compiled at the Johns Hopkins University International Vaccine Access Center (IVAC). Watt et al previously published Hib GBD estimates in 2009 for the year 2000 utilizing data from 1980-2005 [5]. These are now being updated to reflect the increased uptake of Hib vaccine and changes in disease burden in the past 15 years. Using a comprehensive literature search, studies published from 2005 and onward were included in the updated estimates. Broad search criteria were used to identify relevant studies from six global databases (Medline, Embase, CAB Health, Cochrane, Pascal, and Biosis) and four regional databases (African Index Medicus, Index Medicus for the WHO Eastern Mediterranean region, Latin American and Caribbean Health Sciences Information, and Health Literature, Library, and Information Services). Studies used in the previous GBD estimates were manually screened to identify relevant impact studies published before the timeframe of the current literature review. Additionally, Google Scholar was searched for any Hib vaccine impact studies that were not captured in the literature reviews.

Studies were identified as potentially relevant if they reported on Hib vaccine impact on any syndrome in children in an observational setting. Those presenting results from individually-randomized clinical trials were not included, as only the direct effect of the Hib vaccine could be assessed in these trials. More than 40 papers were identified using these criteria. Studies were then excluded if they only provided estimates for specific Hib-related syndromes as opposed to all IHiD, estimates for U5s were not reported or able to be parsed out, pre-vaccination incidence rates were not reported, or

insufficient data were reported to run at least one of the models, as described in Table 2 below. The exclusion process is described in Appendix A. Studies with fewer than two years of post-vaccination data were excluded to acknowledge the disease burden curve and resist attributing greater direct disease reduction in younger age groups to indirect effects. Additionally, if multiple studies presented data from the same country for overlapping time periods, the study with more years of surveillance was chosen. Vaccine coverage level was determined as the percentage of children with three doses of Hib or Hib-containing vaccine; children with fewer than three doses were considered unimmunized. After applying these criteria, 12 studies remained and are described in Table 1 [3, 10, 14, 25-33]. 16 data points were abstracted from these 12 studies, as some studies presented multiple years of post-vaccine introduction data.

Table 1 Characteristics of Observational Trials of Hib Vaccine Included in this Analysis

Study, year	Study location	Study dates	Age range (months)	Vaccine rollout strategy	Years of post-national rollout surveillance	Number of estimates provided
Adegbola, 2005	The Gambia (Western region)	1997-2002	0-59	BC after vaccine efficacy trial	0-3	1
Berndsen, 2011	Iceland	1983-2008	0-59	BC + CUC	0-19	1
CDC, 1994	United States of America	1987-1993	0-59	BC, initially approved in older children	6	1
Cowgill, 2006	Kenya (Kilifi District)	2000-2005	0-59	BC	4	3
Dagan, 1999	Israel	1989-1996	0-59	BC after private market introduction	2	1
Garpenholt, 1996	Sweden	1987-1994	0-59	BC	3	2
Kastrin, 2009	Slovenia	1993-2008	0-59	BC	0-8	1
Kriz, 2005	Czech Republic	1999-2004	0-59	BC	3	2
Ramsay, 2003	United Kingdom	1989-2002	0-59	BC + CUC	0-10	1
Russell, 2009	Kingdom of Tonga	2000-2007	1-59	BC + CUC	2	1
Sigauque, 2013	Mozambique (Manhica District)	2006-2011	0-59	BC	2	1
Singleton, 2005	United States of America (Alaska)	1980-1998	0-59	BC	3	1

BC = birth cohorts

BC + CUC = birth cohorts + catch-up campaign

Analysis Models

A review of the literature was commenced to identify potential methods to evaluate the indirect effects of Hib. A number of techniques were identified; however most were excluded as they required covariates that could not be obtained through a literature review. Three less complex methods were identified and applied to this data. Two of these methods were adapted from previous analyses of Hib vaccine indirect effects and the third from an analysis of hepatitis A vaccine rollout in the United States. Each method is referred to by the first author of the paper in which the method was proposed. The parameters necessary to run each model are included in Table 2. It was not possible to apply all methods to all studies due to the availability of the data needed for each model; however, all methods were applied to at least three point estimates. These methods were then compared to decide which method most completely captured the indirect effects of Hib vaccination. Analyses were completed in STATA (Version 13.0, StataCorp, College Station, Texas).

Wolfson method- In the previous GBD study, IHiD reduction in mature vaccination programs, defined as those in place for more than a year, was regressed against vaccine coverage in U5s to understand how indirect effects changed as population-level coverage increased [5]. We took a similar approach with this analysis, but instead ran a censored regression to account for the restriction of the outcome variable, percent of IHiD reduction, between 0% and 100% [34]. We also defined mature programs as those with at least two years of post-rollout data as opposed to one year. The censored regression, which accounted for direct and indirect vaccine effects, was then compared to the disease reduction expected from direct effects alone. The direct effects

were modeled by a Y = 0.95X line, as Hib vaccine is assumed to have 95% efficacy so 95% of those vaccinated (X) would be protected against IHiD (Y) [2]. Greater disease reduction beyond this threshold could be attributed to indirect effects of the vaccination. The slope of the overall disease reduction curve was strongly positive before 50% coverage but was closer to zero after this point, so a spline term was fit to better represent the curve. By comparing the reduction of disease that had been observed in vaccine impact studies to what would be expected based solely on direct effects of the vaccination, we were able to derive an indirect effects multiplier as a function of vaccine coverage.

Samandari method- Originally, this method was used to examine the indirect effects of routine hepatitis A vaccine rollout in the United States. A series of equations were proposed to measure the indirect protection found in different age groups, as the vaccine was approved for 2-18 year olds but disease reduction was seen in all age groups [35]. To assess the indirect effects seen in the unvaccinated members of the age group that was being vaccinated, Samandari et al provided the equation of

$$I = I_0 (1 - v)^C$$

In this model, I represented the disease incidence after vaccination rollout, I_0 the incidence before vaccination rollout, v the population-level vaccine coverage, and c the indirect effect multiplier. The interpretation of the multiplier was described as the number of children who were effectively protected for each child that was vaccinated. A c of two indicated that two people were effectively protected for each person vaccinated, the person vaccinated and one unvaccinated person. For this analysis, the c coefficient was calculated for each point estimate and then used to obtain a value of I/I_0, or the incidence

rate ratio. The estimated IHiD reduction was then derived from the incidence rate ratio and compared to the vaccine direct effect estimate to calculate the indirect effect multiplier.

Adegbola method- This method was used to examine the indirect effects of Hib vaccine in The Gambia when routine immunization was rolled out in 1997. In order to distinguish the indirect effects from the direct effects of the vaccine, Adegbola et al developed a novel method of calculating vaccine effective coverage that would account for the age distribution of Hib disease in order to estimate how many children were vaccinated early enough to avoid disease [10]. Instead of the standard vaccine effective coverage equation of vaccine efficacy * vaccine coverage, they proposed replacing vaccine coverage with the proportion of cases that would have received direct protection from vaccination early enough to protect against IHiD. This figure was estimated by calculating the proportion of children who were protected through vaccination (with protection deemed complete two weeks after the second dose of Hib vaccine, the point where the vaccine is considered to be effective) before the average age of IHiD invasive disease. The new vaccine effective coverage was then used to calculate the indirect effect multiplier, assumed to be constant across vaccine coverage levels.

Table 2 Parameters Necessary for Inclusion in Each Model

Analysis Name	Data Needed
Wolfson method	Vaccine coverage Percent IHID reduction
Samandari method	Vaccine coverage Pre-vaccination IHiD incidence Post-vaccination IHID incidence
Adegbola method	Average age at second dose Vaccine efficacy Percent IHID reduction

Imputation of Model Parameters

Some model parameters were not explicitly stated in the studies and had to be imputed from various other, reliable sources. Vaccine coverage levels in U5s were very rarely given and often had to be calculated. Most commonly coverage levels were given for children under the age of 1, so U5 coverage was estimated by multiplying this coverage by the number of years that Hib vaccine had been universally given. For example, if coverage was 97% and routine vaccination had been ongoing for three years, the vaccine coverage for U5s was 58.2% [0.97*(3/5)]. National vaccine coverage estimates provided in the study papers was corroborated with what was reported by WHO and UNICEF to ensure accuracy of results [36]. WHO/UNICEF used surveys reporting on the immunization status of children 12-23 months of age to reflect coverage in the previous year's birth cohort [37]. IHiD reduction was calculated using a percent change formula ([pre-vaccination rate- post-vaccination rate]/pre-vaccination rate * 100). These estimates were then checked against the papers that provided IHiD reduction estimates and were identical.

Model Validation and Sensitivity Analyses

A theoretical modelling framework for the analysis of infectious diseases was used to validate the results provided by the three models. Following the principles of an SIR model, Haber et al used vaccine coverage and attack rates in vaccinated and unvaccinated individuals to estimate the basic reproductive number and the reduction of the transmission probability due to direct and indirect effects separately [38]. These parameters were then used to calculate the risk of developing IHiD in the absence and presence of vaccination and the proportion of risk reduction due to indirect effects. We

used the results of two randomized control trials (RCTs) assessing Hib vaccine efficacy to calculate the proportion of disease reduction due to indirect effects and indirect effect multiplier at 10% increments of vaccine coverage. The results were them compared to the outcomes of the Wolfson, Samandari, and Adegbola methods.

The two RCTs chosen were conducted on the Navajo Nation in the Southwestern United States and Finland, two settings with distinct Hib epidemiology [39, 40]. Two RCTs were used as this theoretical framework had not previously been applied to data (personal communication), so it was deemed prudent to ensure that consistent estimates of the indirect effect multiplier were given for separate trials of the same vaccine. Additionally, a "leave one out" sensitivity analysis was performed to ascertain if any single study had an outsized influence on the results. This was done by examining the magnitude of change in the average U5 vaccine coverage as each study was systematically removed from the calculation.

Comparison Paper

One paper was found to have empirically estimated the indirect effects of Hib vaccine for individuals in an American Indian population [16]. The outcomes from our analysis were compared to the results found in the Moulton et al analysis to understand which model most closely approximated the individual indirect effects. This allowed for a better understanding of how population-level observational studies can be best used in the future to approximate the indirect effect results that previously could have only been estimated using a large, cluster-randomized trial.

Results

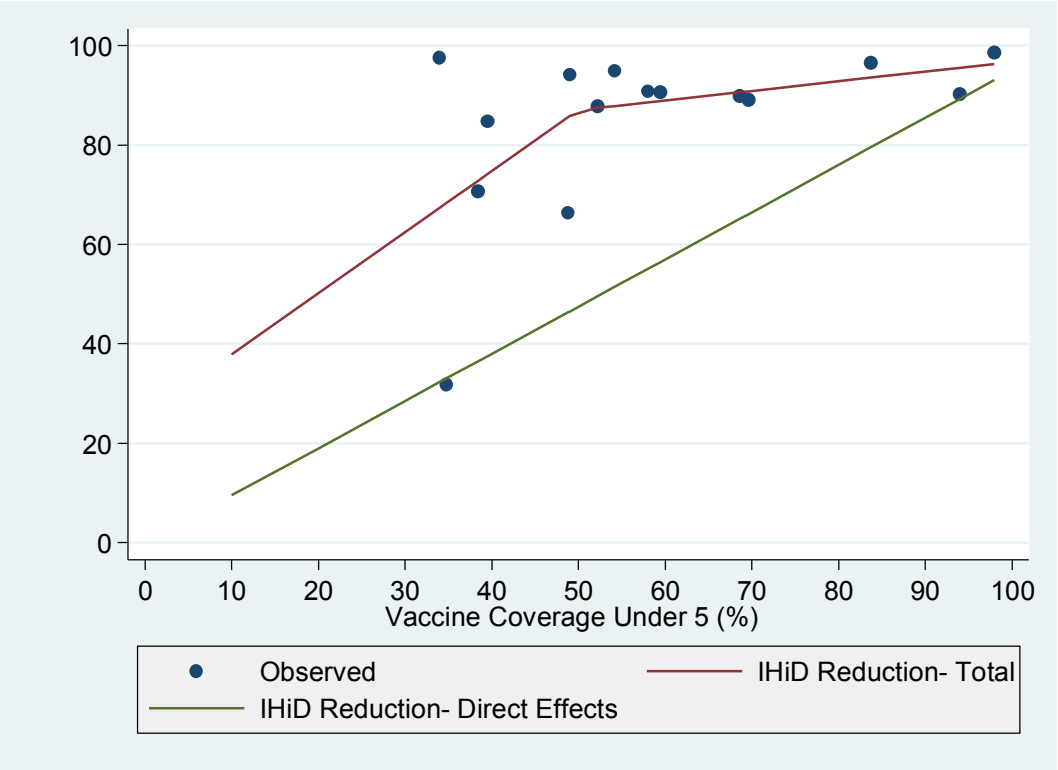
Model Results

Wolfson method- This method showed significant indirect effects at relatively low vaccine coverages, as can be seen in Figure 1. In vaccine coverage levels less than 40%, the percentage IHiD reduction was about twice as great as would be expected due to direct effects alone, after which the indirect effects decreased. This translated into a multiplier ranging from two to four at lower vaccination coverages and then decreasing to about one at higher coverages, indicating that indirect effects for Hib vaccine can start to take hold at coverage levels as low as 10%. Overall, a disease reduction of 85% was seen for vaccine coverage in U5s of 58%. This equation was used to calculate the expected IHiD at specific vaccine coverage levels:

$$\text{For } X < 50,\ Y = (X*1.229922) + 25.58033$$

$$\text{For } X \geq 50,\ Y = (50*1.229922) + ((X-50)*0.191699) + 25.58033$$

Figure 1 Estimated Disease Reduction Due to Indirect Effects- Wolfson



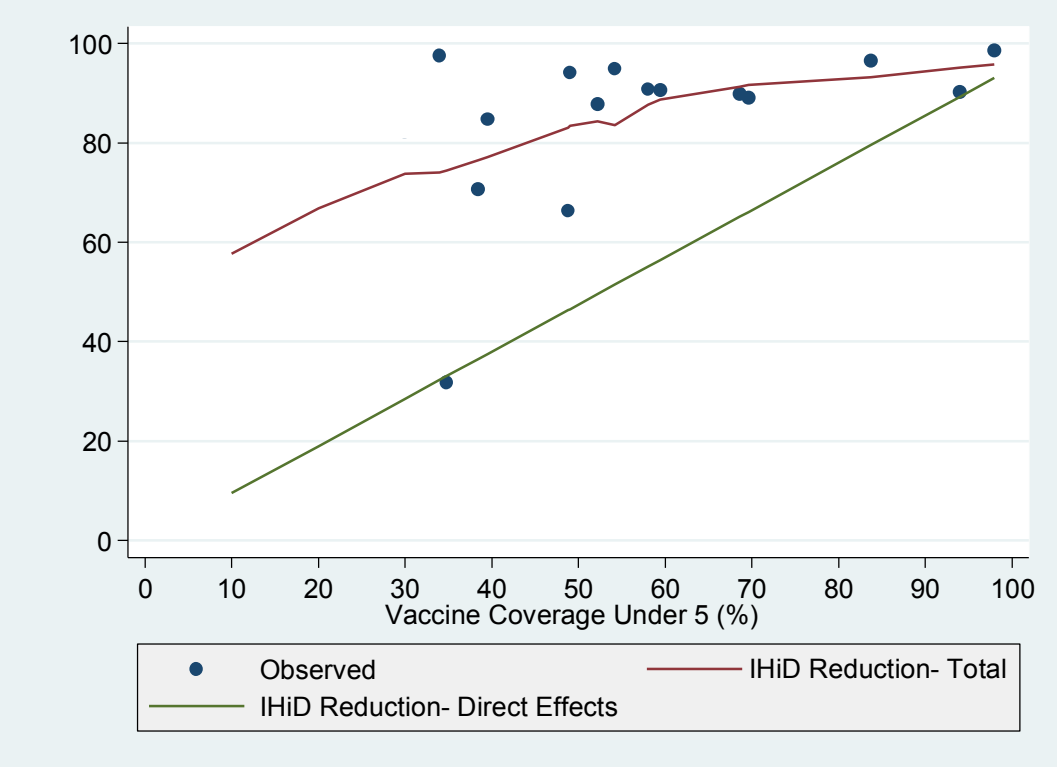
Samandari method- Under these assumptions, indirect effects played a much larger role in disease reduction at lower vaccine coverage than higher coverage levels. To calculate the value of c, the model predicted an equation of

$$c = e \text{ ^((x* -0.0221966) + 2.241278)}$$

This resulted in a c statistic of five or higher for vaccine coverage of 0-30%, rapidly decreasing to below two at 70% coverage and above. The incidence rate ratio and indirect effect multiplier were then calculated. At 10% coverage, the multiplier was estimated to be about six, indicating that five unvaccinated individuals were protected for every vaccinated individual; this decreased to about one at 70% coverage and higher as direct effects began to dominate. A multiplier of 1.1 at 100% coverage was seen due to imperfect vaccine protection. The estimated IHiD reduction was calculated based on vaccine coverage, predicting a 50% decrease at 10% coverage and reaching over 80%

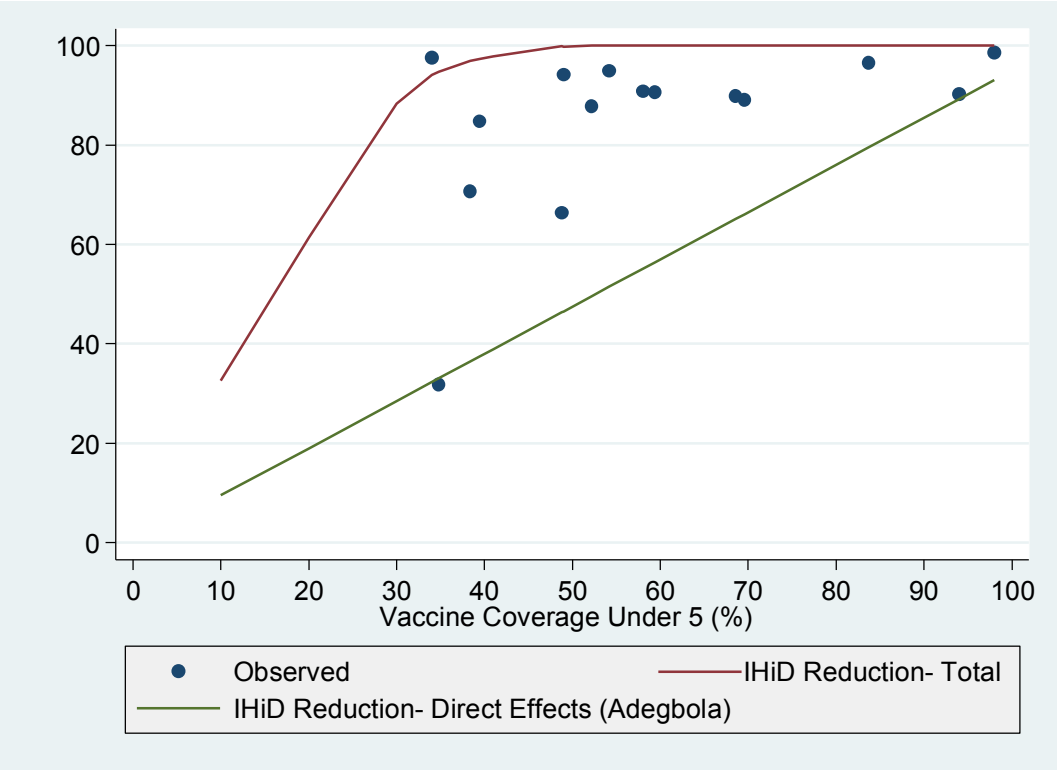
reduction at 30% coverage as shown in Figure 2. After this threshold, the predicted IHiD reduction increased slowly until reaching 100% reduction at 100% coverage.

Figure 2 Estimated Disease Reduction Due to Indirect Effects- Samandari



Adegbola method- Using this method to alternatively calculate the proportion of children directly protected by vaccination, a constant indirect effect multiplier was calculated. Because only three studies provided the necessary parameters for this model, we derived a single multiplier without allowing for variation with vaccine coverage. On average, 30% of children were directly protected from IHiD by vaccination, indicating that the other 70% of disease reduction was due to indirect effects. This resulted in an indirect effect multiplier of 3.3, implying that the majority of protection against IHiD was from indirect effects. Using this multiplier, the model predicted that all IHiD should be eliminated at vaccine coverage levels of 40% or higher as shown in Figure 3 and Table 3.

Figure 3 Estimated Disease Reduction Due to Indirect Effects- Adegbola



At the same level of vaccine coverage, the three models provided varying estimates for the predicted IHiD reduction and indirect effect multiplier. For example at 20% coverage, the predicted IHiD reduction ranged from 50% to almost 75%. These results are presented in Tables 3 and 4 respectively. Although the same trends are reflected in each model as seen in Figure 4, the Wolfson and Samandari methods provide similar IHiD reduction estimates whereas the Adegbola method predicts total disease elimination at much lower vaccine coverage levels. While the Wolfson method never reaches 100% disease reduction, both the Samandari and Adegbola methods do, though at very different coverage levels. The Adegbola method also overestimated the observed data. The indirect effect multiplier estimate varied between the methods as well. While both the Wolfson and Samandari multiplier start higher and decrease to around one at higher vaccine coverage levels, the Adegbola multiplier is constant at approximately

three. The Wolfson and Samandari multipliers similarly average out to about two across all vaccine coverage, but the Adegbola multiplier is almost double that.

Figure 4 Predicted Disease Reduction Due to Indirect Effects- All Methods

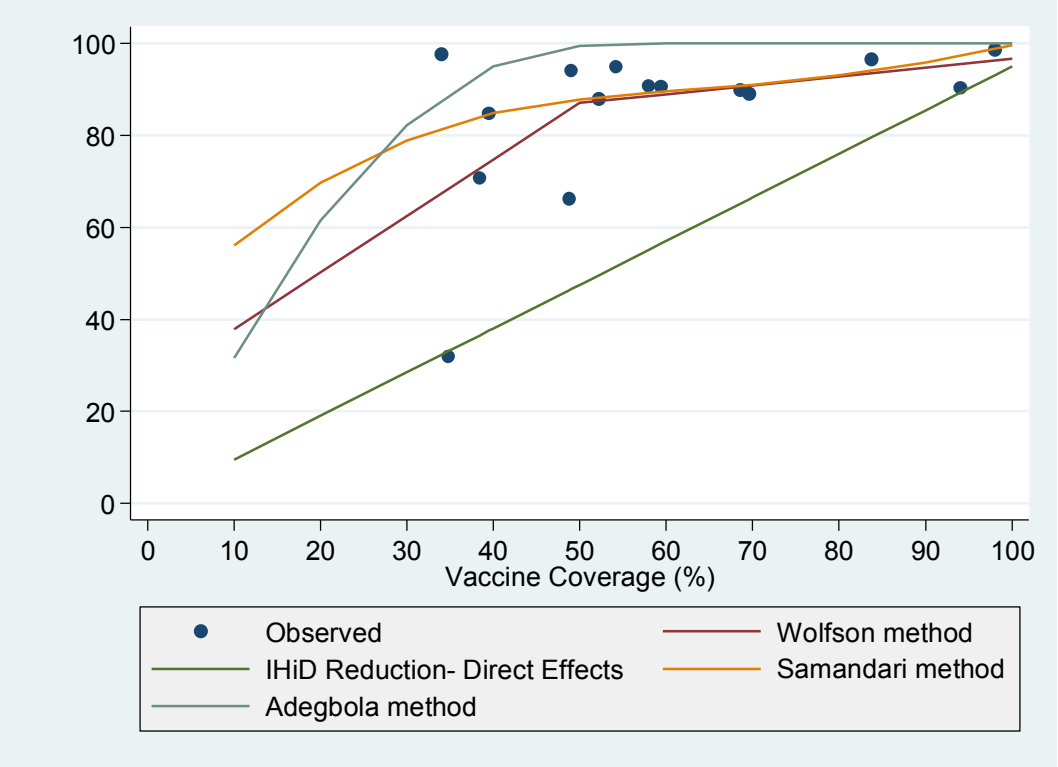


Table 3 Comparison of the Predicted IHiD Reduction (%) Across Methods

Vaccine Coverage	Wolfson method	Samandari method	Adegbola method
10%	37.9	54.8	31.6
20%	50.2	74.0	63.3
30%	62.5	82.2	94.9
40%	74.8	86.2	100.0
50%	87.1	88.3	100.0
60%	89.0	89.7	100.0
70%	90.9	90.9	100.0
80%	92.8	92.3	100.0
90%	94.7	94.7	100.0
100%	96.7	100.0	100.0

Model Validation and Sensitivity Analyses

The Haber et al study provided similar estimates of the indirect effect multiplier to the three methods analyzed here, as shown in Table 4. Both studies analyzed with the Haber et al method produced similar multipliers at varying coverage, indicating the utility of the Haber method as a validation tool. These results were most similar to the Wolfson and Samandari methods, though they also mirrored the outcomes of the Adegbola method at vaccine coverage below 20%. The pattern of a higher multiplier at lower vaccine coverage slowly converging to a multiplier of approximately one at higher coverage levels as direct effects prevail was also observed with the Haber analysis, though these studies reached a multiplier of one at lower coverage levels than the three analysis methods. A comparison of the indirect effect multipliers from the different methods is shown in Figure 5.

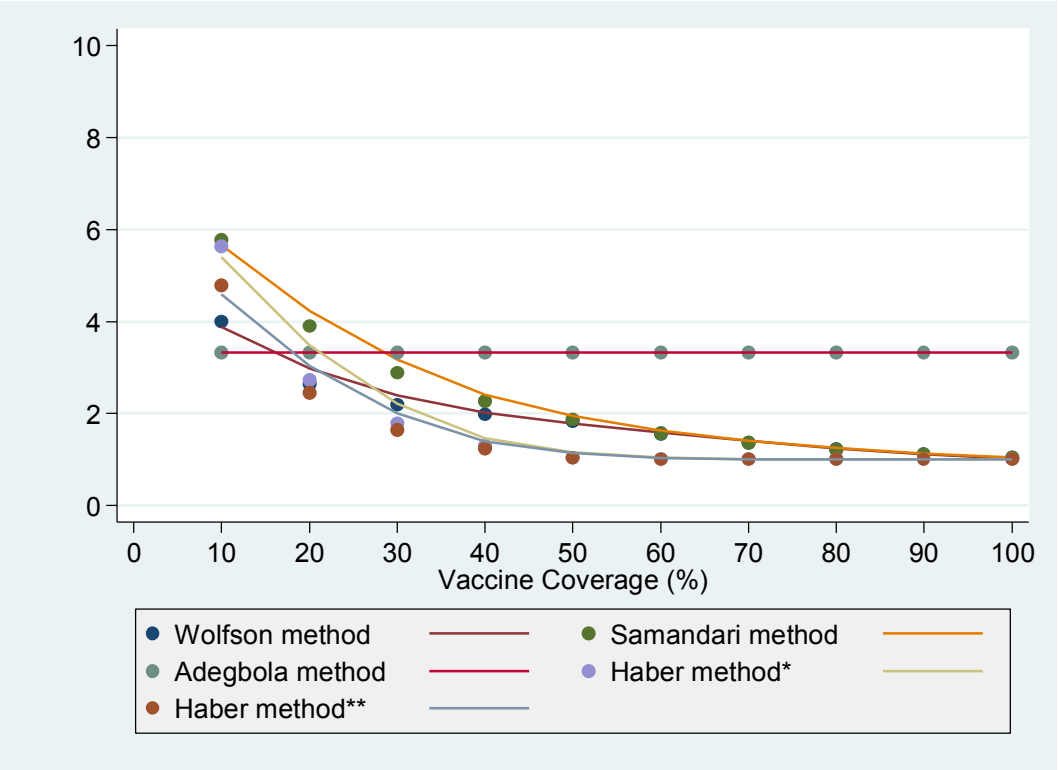
Table 4 Validation of the Indirect Effect Multiplier with the Haber Method

Vaccine Coverage	Wolfson method	Samandari method	Adegbola method	Haber method*	Haber method**
10%	4.0	5.8	3.3	5.6	4.8
20%	2.6	3.9	3.3	2.7	2.5
30%	2.2	2.9	3.3	1.8	1.6
40%	2.0	2.3	3.3	1.3	1.2
50%	1.8	1.9	3.3	1.0	1.0
60%	1.6	1.6	3.3	1.0	1.0
70%	1.4	1.4	3.3	1.0	1.0
80%	1.2	1.2	3.3	1.0	1.0
90%	1.1	1.1	3.3	1.0	1.0
100%	1.0	1.1	3.3	1.0	1.0

* Using Santosham et al study

** Using Eskola et al study

Figure 5 Indirect Effect Multiplier- All Methods



From the "leave one out" sensitivity analysis, one estimate was identified as overly influential of the results. Compared to the overall average U5 vaccination coverage of 58%, excluding the Cowgill et al estimate for two years of post-vaccination data decreased the average U5 vaccination coverage to 20%. However, the Cowgill et al study provided two additional estimates for three and four years of post-vaccination data that were used in the models and were not excessively influential on the results. The CDC study was the least influential, decreasing the average U5 vaccination coverage to 53% from 58%.

Model Results and the Comparison Paper

In their analysis of Hib vaccine herd effects in Navajo children, Moulton et al. compared the risk reduction of living in areas with certain levels of vaccination coverage

in children under the age of two [16]. Using 20% vaccine coverage increments, they observed significant risk reductions for children living in areas with 20-39% coverage and 40-59% coverage when compared to those living in areas with < 20% coverage. In areas with greater than 60% coverage, they saw a large increase in IHiD risk, though this was not statistically significant and attributed to a dearth of cases in high coverage settings. It was expected that our analysis would provide slightly lower risk reductions because of our focus on U5s as opposed to children under the age of two years. The Wolfson and Samandari methods produced similar risk reductions to the Moulton method below 60% vaccinated, but the Adegbola method predicted much greater reductions as seen in Table 5. As the Moulton paper empirically investigated the indirect protection provided by communities to individuals, the results are most likely a good estimator of the true risk reduction associated with vaccination.

Table 5 Comparison to Moulton IHiD Risk Reductions

Vaccine Coverage	Moulton paper	Wolfson method	Samandari method	Adegbola method
20-39%	56.5	44.0	55.5	73.1
40-59%	73.2	78.6	69.2	100.0
60-79%	-167	85.5	76.4	100.0
80-99%	-521	92.3	92.6	100.0

Discussion

Model Comparisons

Indirect effects have long been observed with vaccine programs, but are rarely measured. As this type of research is sparse, it was deemed necessary to compare different analytic methods and identify the ones that best approximated the disease reduction seen in real-world vaccine rollout scenarios. Multiple validation techniques and sensitivity analyses were also employed to ensure that the methods were correctly capturing the relationship between vaccine coverage and indirect protection. After searching the literature, we identified four methods that had previously been used to analyze primary data to better understand the impact of indirect effects on total immunity. Three of these methods were used in the original analysis, while the final method, a theoretical framework, was used for validation.

All three of the methods used here were created to model infectious diseases that have high incidence in children. However the Samandari and Adegbola methods were developed to examine individual level data, not the group level data that we were using for this analysis. The Wolfson method was specifically developed for this type of data. Looking at Figures 4 and 5, it seems that all of the methods, with the exception of the Adegbola method, produced similar results. Although each method was developed with different assumptions and dynamics in mind, the Wolfson and Samandari methods estimated indirect effects similarly.

Each of the models has strengths and weaknesses, but it seems that the Wolfson and Samandari methods most accurately measured indirect effects, as judged by their similarity to the Moulton estimates. The parameters needed for both methods are minimal and easily available, and validation with the Haber method demonstrated the consistency

of both of these methods. It seems likely that the two methods could be applied in different settings. Because the Wolfson method requires multiple pre-post studies, this could be a useful method to assess indirect effects in vaccines that are already being used. The Samandari method could alternatively be helpful in a setting where a vaccine program is being implemented for the first time.

One of the most striking aspects of this analysis is the existence of significant indirect protection at low levels of vaccine coverage. While most vaccines likely provide some degree of indirect protection at low vaccine coverage due to the reduction in the pool of susceptibles, it is negligible on a population level [41]. However, the ability of Hib conjugate vaccine to reduce nasopharyngeal colonization leads to significant indirect protection, providing noticeable protection at low vaccine coverage. These low levels of coverage can easily be achieved through private market introduction without routine vaccination and has been shown to lead to drastic disease reductions; this is despite low coverage and better risk profile of vaccine recipients in exclusively private market settings [14].

Strengths and Limitations

This analysis had a number of strengths that increased both the reliability and validity of the results. Twelve studies were included from many parts of the world, with only four from the United States and Western Europe. Previous analyses of vaccines have focused exclusively on these high-income, low-burden settings, drawing concerns about their external validity. Post-vaccination data also ranged from two to nineteen years after introduction into routine vaccination programs, representing almost the entire time since the licensure of Hib conjugate vaccine. Additionally, the comparison of multiple models,

as well as validation and the results of the sensitivity analysis, increase confidence that the results may reflect the reality of indirect protection from Hib conjugate vaccine.

Despite these strengths, there are a number of limitations that could have affected our final results. Incidence rates are almost certainly underestimated in all of these studies, as they did not capture infections that were not seen in healthcare facilities. However, it is likely that incidence was underestimated both before and after vaccine introduction, so calculated disease reduction is likely to be less biased. There was also some discrepancy between models regarding the level of vaccine coverage required for IHiD elimination, with most estimating that almost 100% coverage would be necessary to completely eliminate disease. However, in practice we have seen complete elimination of disease with coverage levels as low as 60%, and our models indicate greater than 90% disease reduction at 60% coverage [10]. This difference could be due to the lack of studies with less than 20% coverage and only four estimates with coverage below 40%. Although our exclusion of studies with few years of post-vaccination data was necessary to account for the disease burden curve, this could have biased our results.

The need to assess indirect effects over years of rollout leaves open the possibility that IHiD reduction could be due, at least in part, to secular trends. Fortunately, many studies acknowledged this possibility and also tracked rates of invasive pneumococcal disease in settings where the pneumococcal conjugate vaccine had not yet been introduced. They did not observe significant changes in pneumococcal disease during the time period of rapid IHiD disease reduction, indicating that secular trends did not play a large role in disease reduction. The small number of studies also precluded us from calculating meaningful confidence intervals around the indirect effect multiplier

estimates, though we did examine the changes in standard error with the "leave one out" analysis.

Future Directions

Overall, this analysis has a number of real world and future research implications. Currently, critical vaccination thresholds used for disease elimination estimates are calculated as $1 - 1/R_0$ [12, 41]. However the value of R_0 is theoretical and difficult to conclusively determine. Using the methods described here, a critical vaccination threshold could be estimated based on real world data, leading to a more accurate idea of the level of vaccination necessary to achieve Hib elimination. This would allow for more efficient allocation of resources to vaccination programs. The methods used here could also be applied to other vaccines, such as pneumococcal conjugate vaccine, to better understand the indirect protection provided and more accurately estimate the population protection provided by these vaccines. A better understanding of the full protection of vaccinations will allow policy makers to more confidently invest in vaccination programs. It is evident from our analysis that significant disease reduction is possible without prohibitively high vaccine coverage figures. We hope that these estimates will encourage policy makers to make decisions that will drastically decrease, and eventually eliminate, Hib disease.

References

1. (WHO), W.H.O., *Global literature review of Haemophilus influenzae type b and Streptococcus pneumoniae invasive disease among children less than five years of age 1980–2005*. 2009.
2. (CDC), C.f.D.C.a.P., *Haemophilus influenzae type b*. 2009, *Epidemiology and Prevention of Vaccine-Preventable Diseases (The Pink Book)*: *Washington, DC: Public Health Foundation*. p. 71-84.
3. Cowgill, K.D., et al., *Effectiveness of Haemophilus influenzae type b Conjugate vaccine introduction into routine childhood immunization in Kenya.* JAMA, 2006. **296**(6): p. 671-8.
4. Lozano, R., et al., *Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010.* Lancet, 2012. **380**(9859): p. 2095-128.
5. Watt, J.P., et al., *Burden of disease caused by Haemophilus influenzae type b in children younger than 5 years: global estimates.* Lancet, 2009. **374**(9693): p. 903-11.
6. Millar, E.V., et al., *Toward elimination of Haemophilus influenzae type B carriage and disease among high-risk American Indian children.* Am J Public Health, 2000. **90**(10): p. 1550-4.
7. Bower, C., et al., *Measuring the impact of conjugate vaccines on invasive Haemophilus influenzae type b infection in Western Australia.* Aust N Z J Public Health, 1998. **22**(1): p. 67-72.
8. Gessner, B.D., et al., *Incidences of vaccine-preventable Haemophilus influenzae*

type b pneumonia and meningitis in Indonesian children: hamlet-randomised vaccine-probe trial. Lancet, 2005. **365**(9453): p. 43-52.

9. Mulholland, K., et al., *Randomised trial of Haemophilus influenzae type-b tetanus protein conjugate vaccine [corrected] for prevention of pneumonia and meningitis in Gambian infants.* Lancet, 1997. **349**(9060): p. 1191-7.
10. Adegbola, R.A., et al., *Elimination of Haemophilus influenzae type b (Hib) disease from The Gambia after the introduction of routine immunisation with a Hib conjugate vaccine: a prospective study.* Lancet, 2005. **366**(9480): p. 144-50.
11. Lewis, R.F., et al., *Action for child survival: elimination of Haemophilus influenzae type b meningitis in Uganda.* Bull World Health Organ, 2008. **86**(4): p. 292-301.
12. Anderson, R.M. and R.M. May, *Vaccination and herd immunity to infectious diseases.* Nature, 1985. **318**(6044): p. 323-9.
13. Hviid, A. and M. Melbye, *Impact of routine vaccination with a conjugate Haemophilus influenzae type b vaccine.* Vaccine, 2004. **22**(3-4): p. 378-82.
14. Dagan, R., et al., *Effectiveness of a nationwide infant immunization program against Haemophilus influenzae b. The Israeli Pediatric Bacteremia and Meningitis Group.* Vaccine, 1999. **17**(2): p. 134-41.
15. Peltola, H., T. Kilpi, and M. Anttila, *Rapid disappearance of Haemophilus influenzae type b meningitis after routine childhood immunisation with conjugate vaccines.* Lancet, 1992. **340**(8819): p. 592-4.
16. Moulton, L.H., et al., *Estimation of the indirect effect of Haemophilus influenzae type b conjugate vaccine in an American Indian population.* Int J Epidemiol,

2000. **29**(4): p. 753-6.

17. Cisse, M.F., et al., *The Elimination of Haemophilus influenzae type b meningitis following conjugate vaccine introduction in Senegal.* Pediatr Infect Dis J, 2010. **29**(6): p. 499-503.

18. Michaels, R.H., et al., *Factors affecting pharyngeal Haemophilus influenzae type b colonization rates in children.* J Clin Microbiol, 1976. **4**(5): p. 413-7.

19. Granoff, D.M. and R.S. Daum, *Spread of Haemophilus influenzae type b: recent epidemiologic and therapeutic considerations.* J Pediatr, 1980. **97**(5): p. 854-60.

20. Barbour, M.L., et al., *The impact of conjugate vaccine on carriage of Haemophilus influenzae type b.* J Infect Dis, 1995. **171**(1): p. 93-8.

21. Chen, W.J., et al., *Estimation of the herd protection of Haemophilus influenzae type b conjugate vaccine against radiologically confirmed pneumonia in children under 2 years old in Dhaka, Bangladesh.* Vaccine, 2014. **32**(8): p. 944-8.

22. Halloran, M.E., et al., *Direct and indirect effects in vaccine efficacy and effectiveness.* Am J Epidemiol, 1991. **133**(4): p. 323-31.

23. Hayes, R.J. and S. Bennett, *Simple sample size calculation for cluster-randomized trials.* Int J Epidemiol, 1999. **28**(2): p. 319-26.

24. *The Gambia Hepatitis Intervention Study. The Gambia Hepatitis Study Group.* Cancer Res, 1987. **47**(21): p. 5782-7.

25. (CDC), C.f.D.C.a.P., *Progress toward elimination of Haemophilus influenzae type b disease among infants and children--United States, 1987-1993.* MMWR Morb Mortal Wkly Rep, 1994. **43**(8): p. 144-8.

26. Berndsen, M.R., H. Erlendsdóttir, and M. Gottfredsson, *Evolving epidemiology of*

invasive Haemophilus infections in the post-vaccination era: results from a long-term population-based study. Clin Microbiol Infect, 2012. **18**(9): p. 918-23.

27. Garpenholt, O., et al., *The impact of Haemophilus influenzae type b vaccination in Sweden.* Scand J Infect Dis, 1996. **28**(2): p. 165-9.

28. Kastrin, T., et al., *Characterisation of invasive Haemophilus influenzae isolates in Slovenia, 1993-2008.* Eur J Clin Microbiol Infect Dis, 2010. **29**(6): p. 661-8.

29. Kriz, P., V. Lebedova, and C. Benes, *Large decrease in incidence of invasive Haemophilus influenzae b disease following introduction of routine vaccination in the Czech Republic.* Euro Surveill, 2005. **10**(7): p. E050728.4.

30. Ramsay, M.E., et al., *Estimating Haemophilus influenzae type b vaccine effectiveness in England and Wales by use of the screening method.* J Infect Dis, 2003. **188**(4): p. 481-5.

31. Russell, F.M., et al., *Reduction of meningitis and impact on under-5 pneumonia after introducing the Hib vaccine in the Kingdom of Tonga.* Ann Trop Paediatr, 2009. **29**(2): p. 111-7.

32. Sigaúque, B., et al., *Haemophilus influenzae type b disease among children in rural Mozambique: impact of vaccine introduction.* J Pediatr, 2013. **163**(1 Suppl): p. S19-24.

33. Singleton, R., et al., *Experience with the prevention of invasive Haemophilus influenzae type b disease by vaccination in Alaska: the impact of persistent oropharyngeal carriage.* J Pediatr, 2000. **137**(3): p. 313-20.

34. Long, J.S., *Regression models for categorical and limited dependent variables*. Advanced quantitative techniques in the social sciences. 1997, Thousand Oaks:

Sage Publications. xxx, 297 p.

35. Samandari, T., B.P. Bell, and G.L. Armstrong, *Quantifying the impact of hepatitis A immunization in the United States, 1995-2001.* Vaccine, 2004. **22**(31-32): p. 4342-50.

36. United Nations, D.o.E.a.S.A., *World Population Prospects: The 2012 Revision.* 2012.

37. Burton, A., et al., *WHO and UNICEF estimates of national infant immunization coverage: methods and processes.* Bull World Health Organ, 2009. **87**(7): p. 535-41.

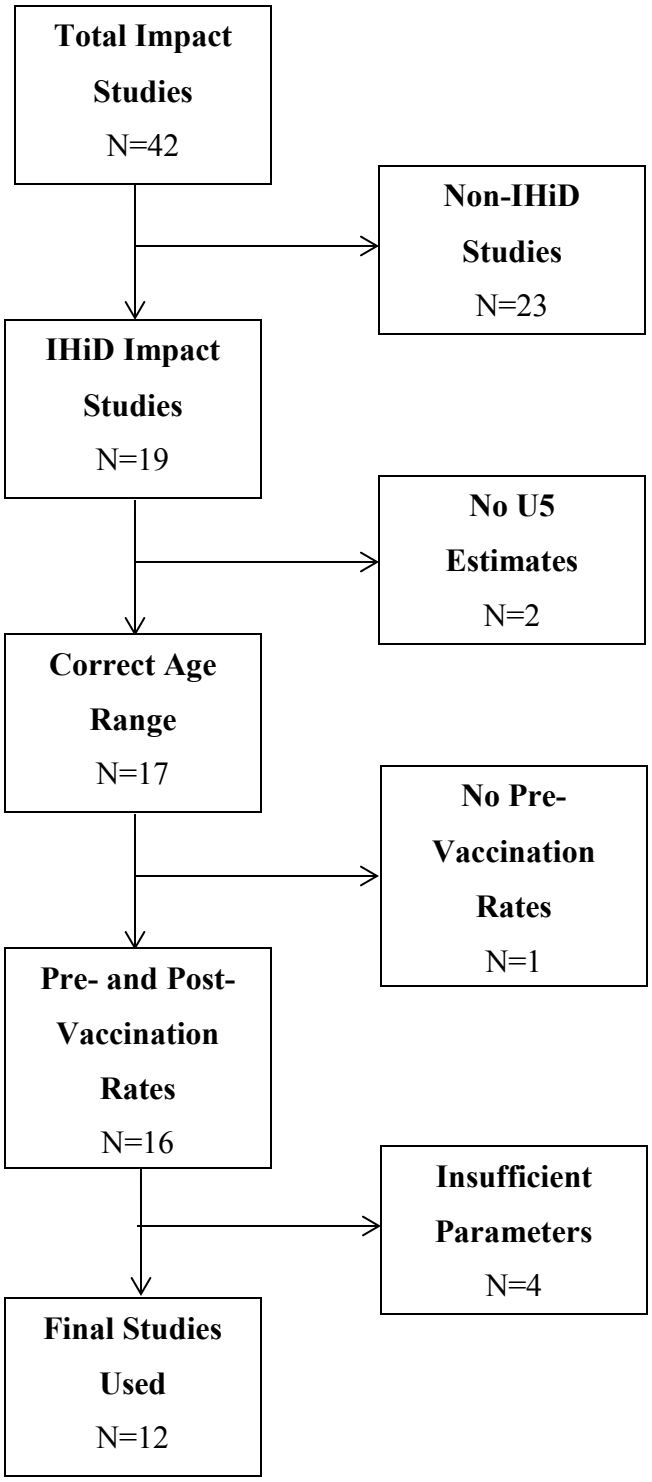
38. Haber, M., *Estimation of the direct and indirect effects of vaccination.* Stat Med, 1999. **18**(16): p. 2101-9.

39. Santosham, M., et al., *The efficacy in Navajo infants of a conjugate vaccine consisting of Haemophilus influenzae type b polysaccharide and Neisseria meningitidis outer-membrane protein complex.* N Engl J Med, 1991. **324**(25): p. 1767-72.

40. Eskola, J., et al., *A randomized, prospective field trial of a conjugate vaccine in the protection of infants and young children against invasive Haemophilus influenzae type b disease.* N Engl J Med, 1990. **323**(20): p. 1381-7.

41. Fine, P.E., *Herd immunity: history, theory, practice.* Epidemiol Rev, 1993. **15**(2): p. 265-302.

Appendix A


Total Impact Studies
N=42
Non-IHiD Studies
N=23
IHiD Impact Studies
N=19
No U5 Estimates
N=2
Correct Age Range
N=17
No Pre-Vaccination Rates
N=1
Pre- and Post-Vaccination Rates
N=16
Insufficient Parameters
N=4
Final Studies Used
N=12

Curriculum Vitae

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EDUCATION

Johns Hopkins Bloomberg School of Public Health | Baltimore, MD
Expected May 2015
Masters of Health Sciences in Epidemiology GPA: 3.88
Concentration: Infectious Disease Epidemiology
Certificate: Vaccine Science and Policy
Thesis: Quantifying the Indirect Effects of Haemophilus influenzae type b Vaccination in Children Under 5 Years-Old
Funding: Masters' Tuition Scholarship and Global Health Established Field Placement

Washington University in St. Louis | St. Louis, MO 2009- 2012
Bachelor of Arts in Psychology and Public Health GPA: 3.58
Honors: College Honors, Dean's List Recipient Fall 2009, Fall 2011, & Spring 2012

RESEARCH/WORK EXPERIENCE

Lead Data Abstractor June 2014- present
International Vaccine Access Center (IVAC) | JHBSPH | Baltimore, MD

- Screen 12,000+ articles for potential inclusion into global childhood morbidity and mortality estimates for *Haemophilus influenzae* type b (Hib) and *Streptococcus pneumoniae*
- Abstract data from more than 1,000 scholarly articles
- Perform analyses to determine indirect effect estimates based on vaccination coverage to be used in disease burden modeling

Student Research Assistant September 2013- present
Center for American Indian Health (CAIH) | JHBSPH | Baltimore, MD

- Perform data analyses for a Phase II clinical trial (GSK Study ID 115597) of a pneumococcal protein vaccine on acute otitis media in Native American infants on the Navajo and White Mountain Apache reservations, estimating direct and indirect vaccine impact
- Analyze Active Bacterial Core data to examine trends over time in Invasive Pneumococcal Disease (IPD) incidence and antimicrobial resistance in invasive pneumococcal isolates and hospitalizations due to IPD from the Navajo Nation

Global Health Established Field Placement Fellow May 2014- August 2014
Perinatal HIV Research Unit (PHRU) | University of the Witwatersrand | Johannesburg, South Africa

- Initiated a prevalence study of active tuberculosis among diabetes patients at Chris Hani Baragwanath Hospital in Soweto, South Africa; interviewed 150+ patients
- Created source forms, set up database, and trained all interviewers
- Completed a previous medical record abstraction study to ascertain the incidence of previous active TB cases in all diabetic patients currently seen at the hospital

Professional Rater I June 2012- June 2013
GERS Study | Washington University School of Medicine | St. Louis, MO

- Conducted phone interviews with over 600 previous participants of a smoking cessation study to ascertain their cigarette smoking and quitting behavior
- Assisted with primary data analysis and paper writing and editing
- Provided smoking cessation counseling for post-myocardial infarction patients in a feasibility trial involving randomized nicotine replacement therapy and regular cessation counseling

Public Health Summer Fellow May 2011- August 2011
Project: IMHOTEP | NIOSH/CDC **|** Cincinnati, OH/Atlanta, GA

- Collaborated with the National Institute for Occupational Safety and Health (NIOSH) on development and testing of a curriculum to educate young agricultural workers about their rights and responsibilities at work; this curriculum was adapted to state-specific laws
- Formed a focus group of local 4H club members to test the efficacy of the curriculum
- Received the Marvin Mills Award for best Occupational Health project

BUSINESS EXPERIENCE

Social Innovation Lab Cohort member October 2014- present
Social Innovation Lab | Johns Hopkins University | Baltimore, MD

- Selected as one of twelve projects to receive $1,000 in seed money, mentorship, and resources to bring an innovative idea to fruition
- Plan to develop and market mustard seed pillows, used in India for centuries, as a cheap and noninvasive method of encouraging proper newborn skull development

TEACHING EXPERIENCE

- **Teaching Assistant:** Concepts and Methods in Infectious Disease Epidemiology (JHBSPH); Epidemiologic Methods II (JHBSPH)
- **Tutor:** Epidemiologic Methods I (JHBSPH)

PRESENTATIONS

Annual Biomedical Research Conference for Minority Students
St. Louis, MO November, 2011

- Presented a poster about summer research from the Project: IMHOTEP program (described above)

PROFESSIONAL DEVELOPMENT

Computer Skills: Proficient with Microsoft Office, Excel, and PowerPoint; Proficient with STATA 13.0; Experience with SPSS, SAS 9.2, and R-3.1.1; Proficient with REDCap, EndNote X7
Languages: Bengali (Fluent)
Travel Abroad: Belgium, Canada, France, India, Mexico, Morocco, Spain, South Africa, Thailand, UK